

(12)

EUROPEAN PATENT APPLICATION

(21) Application number: 81300431.4

(22) Date of filing: 02.02.81

(51) Int. Cl.³: **C 07 C 143/78**
C 07 C 147/14, C 07 C 149/453
A 61 K 31/18

(30) Priority: 08.02.80 JP 14382/80

(43) Date of publication of application:
 26.08.81 Bulletin 81/34

(84) Designated Contracting States:
 AT BE CH DE FR GB IT LI LU NL SE

(71) Applicant: YAMANOUCHI PHARMACEUTICAL CO. LTD.
 No. 5-1 Nihonbashi-Honcho, 2-chome Chuo-ku
 Tokyo(JP)

(72) Inventor: Imai, Kazuo
 No.2-880, Mihashi
 Omiya-shi Saitama(JP)

(72) Inventor: Niigata, Kunihiro
 No. 18-21, Fujimi 2-chome
 Ageo-shi Saitama(JP)

(72) Inventor: Fujikura, Takashi
 No. 3-17, Shirahata 4-chome
 Urawa-shi Saitama(JP)

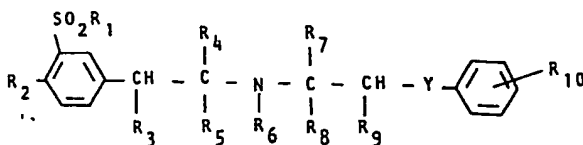
(72) Inventor: Hashimoto, Shinichi
 No. 1067-1, Ohashi
 Matsudo-shi Chiba(JP)

(72) Inventor: Takenaka, Toichi
 No. 27-H-1108, Nakadai 3-chome Itabashi-ku
 Tokyo(JP)

(74) Representative: Geering, Keith Edwin et al.
 REDDIE & GROSE 16 Theobalds Road
 London WC1X 8PL(GB)

(54) Sulfamoyl-substituted phenethylamine derivatives, their preparation, and pharmaceutical compositions, containing them.

(57) A sulfamoyl-substituted phenethylamine derivate represented by the general formula



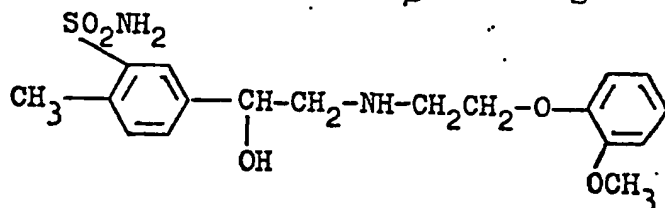
wherein R₁ represents an amino group or a mono- or di-lower alkylamino group; R₂ represents a hydroxyl group, a lower alkyl group, or a lower alkoxy group; R₃ represents hydrogen, halogen, a lower alkyl group, a lower alkoxy group, a phenylthio group, or a phenylsulfinyl group; R₄, R₅, R₆, R₇, R₈, and R₉ are selected independently from hydrogen and lower alkyl groups; R₁₀ represents hydrogen, a lower alkyl group, or a lower alkoxy group; and Y represents oxygen or a methylene group and is oxygen when R₂ is a hydroxyl group; or a salt thereof. The compounds exhibit α -adrenergic blocking action and are useful as antihypertensive agents and for the treatment of congestive heart failure. In the preferred compounds according to the invention R₃ is hydrogen or lower alkyl.

SULFAMOYL-SUBSTITUTED PHENETHYLAMINE
DERIVATIVES, THEIR PREPARATION, AND
PHARMACEUTICAL COMPOSITIONS, CONTAINING
THEM

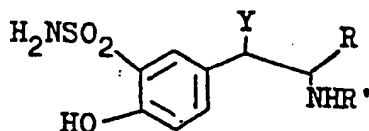
This invention relates to sulfamoyl-substituted phenethyl-amine derivatives and acid addition salts thereof, their preparation, and their pharmaceutical use. Compounds according to the invention exhibit α -adrenergic blocking action and can be used as antihypertensive agents and for treating congestive heart failure.

British Patent No. 2,006,772 discloses a series of compounds exhibiting α - and β -adrenergic blocking actions and

that the compound shown by the following formula exhibits strong α - and β -adrenergic blocking actions



U. S. Patent No. 3,860,647 discloses a series of compounds shown by the following general formula



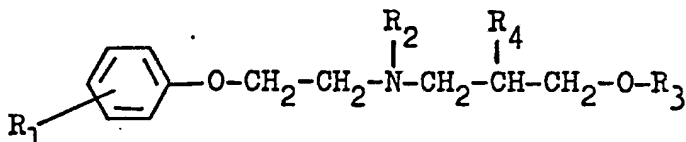
wherein R represents hydrogen or alkyl having 1-4 carbon atoms;

R' represents alkyl having 1-6 carbon atoms, cycloalkyl

having 3-6 carbon atoms, $\text{XC}_6\text{H}_4(\text{CH}_2)_2\text{CH}(\text{CH}_3)$, $\text{XC}_6\text{H}_4(\text{CH}_2)_2\text{C}(\text{CH}_3)_2$, $\text{XC}_6\text{H}_4\text{CH}_2\text{CH}(\text{CH}_3)$, or $\text{XC}_6\text{H}_4\text{CH}_2\text{C}(\text{CH}_3)_2$ (wherein X represents

hydrogen, hydroxyl or methoxy); and Y represents hydrogen or hydroxy. It is disclosed in this U.S. Patent that these compounds exhibit β -adrenergic blocking action.

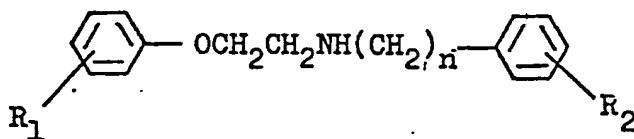
British Patent No. 902,617 discloses a series of compounds shown by the following general formula



wherein R_1 is hydroxyl, methyl, methoxy, etc.; R_2 is hydrogen, methyl, etc.; R_3 is phenyl, benzyl or a hydroxy-, methyl-, methoxy-, ethoxy-, chloro- or bromo-substituted phenyl or benzyl radical, etc.; and R_4 is hydrogen, etc.

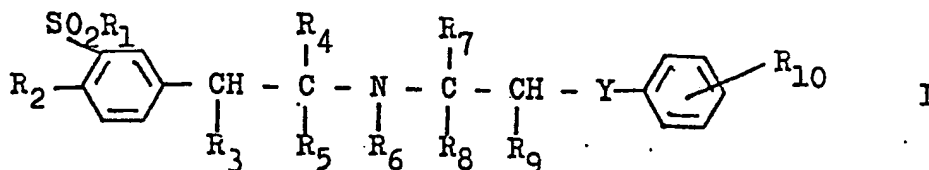
These compounds exhibit α -adrenergic blocking action (see, "J. Med. Chem."; 9, 812-818(1966)) and possess antihypertensive activity.

Also, in "J. Med. Chem."; 9, 812-818(1966), it is disclosed that the phenoxyethylamine-type compounds shown by the following general formula possess α -adrenergic blocking action



wherein R_1 represents o- OCH_3 , etc., and R_2 represents o- or p- OCH_3 , etc.

According to this invention there are provided sulfamoyl-substituted phenethylamine derivatives shown by following general formula I:



wherein R_1 represents an amino group or a mono- or di-lower alkylamino group; R_2 represents a hydroxyl group, a lower alkyl group, or a lower alkoxy group; R_3 represents hydrogen, halogen, a lower alkyl group, a lower alkoxy group, a phenylthio group, or a phenylsulfinyl group; R_4 , R_5 , R_6 , R_7 , R_8 and R_9 are selected independently from hydrogen and lower alkyl groups; R_{10} represents hydrogen, a lower alkyl group, or a lower alkoxy group; and Y represents oxygen or a methylene group and is oxygen when R_2 is a hydroxyl group; and acid addition salts thereof.

The term "lower" used herein means a straight or branched carbon chain having 1 to 5 carbon atoms. For example, "lower alkyl group" includes methyl, ethyl, propyl, butyl, pentyl and isobutyl groups, etc.; and "lower alkoxy group" includes methoxy, ethoxy, propoxy and butoxy groups, etc.

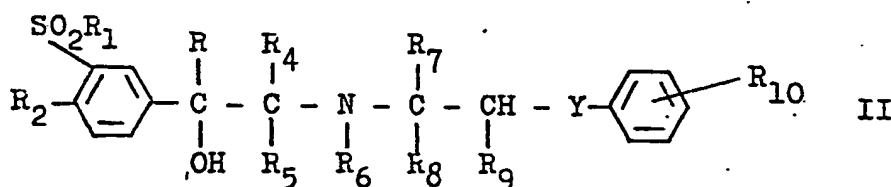
Also, in the above-described formula, R_{10} which is a substituent of the benzene ring may be disposed at any position ortho-, meta- or para-to the side chain. Furthermore, since the compounds of this invention shown by formula I can readily
 5 form salts and contain asymmetric carbon atom(s), the invention includes the salts thereof, and any optically active or inactive isomer or isomer mixture thereof.

The compounds of the present invention exhibit α -
 10 adrenergic blocking action and thus can be utilized for various treatments. For example, they can be used for the treatment of hypertension, congestive heart failure, angina pectoris, lower urinary tract dysfunction, prostatic hypertrophy, pheochromocytoma and peripheral vascular
 15 disorders.

The compounds of this invention shown by formula I can be produced by the following processes.

Process 1:

A compound of formula I is obtainable by reacting a
 20 compound shown by general formula II

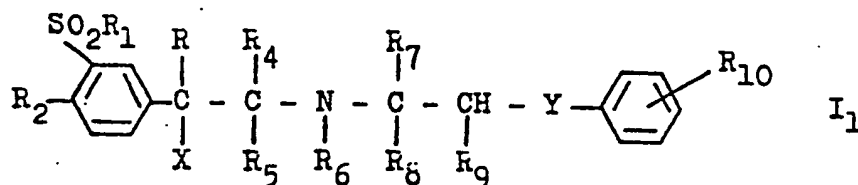


wherein R represents hydrogen or a lower alkyl group and

$R_1, R_2, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}$ and Y have the same significance as in formula I

with halogenating agent and then, if desired, (a) reducing the halogenated product obtained by the above reaction; or (b) reacting the halogenated product with alkaline material and then
 /reacting the product thus obtained with hydrogen iodide, a lower alcohol, or thiophenol, and further, if desired, oxidizing the product obtained by the reaction with thiophenol.

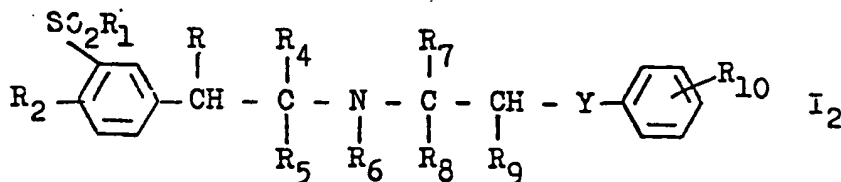
In process I a starting material shown by formula II described above can be reacted with halogenating agent to provide a product shown by general formula I_1



wherein X represents chlorine or bromine and R, $R_1, R_2, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}$ and Y have the same significance as in formula II

and then, if desired, (a) the halogenated product shown by formula I_1 is reduced to form a compound shown by formula

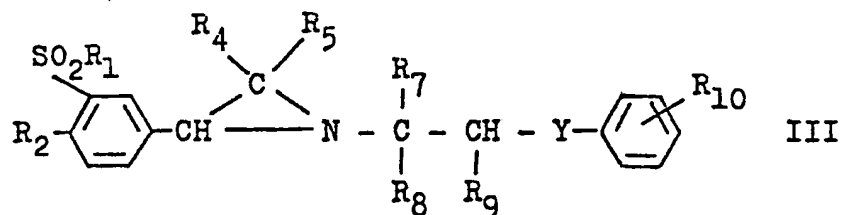
I_2



wherein R, $R_1, R_2, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}$ and Y have the same significance as above described;

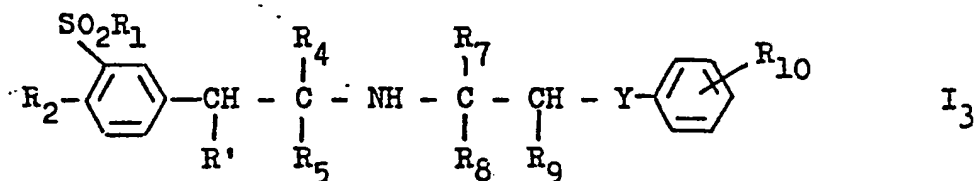
or (b) the halogenated product shown by formula I_1 is treated with alkaline material to form the aziridine compound shown

by following general formula III



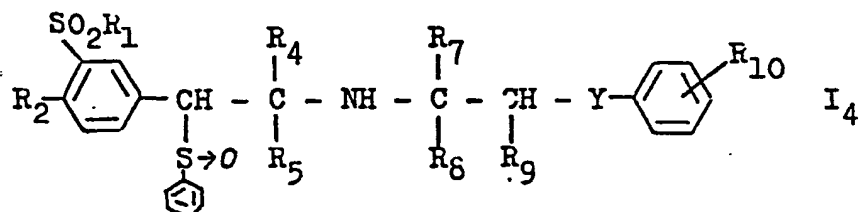
wherein R_1 , R_2 , R_4 , R_5 , R_7 , R_8 , R_9 , R_{10} and Y have the same significance as above described, and

then the aziridine compound is reacted with hydrogen iodide,
 5 a lower alcohol, or thiophenol to provide the compound shown
 by general formula I₃



wherein R' represents iodine, a lower alkoxy group or a phenylthio group and R_1 , R_2 , R_4 , R_5 , R_7 , R_8 , R_9 , R_{10} and Y have the same significance as above described ;

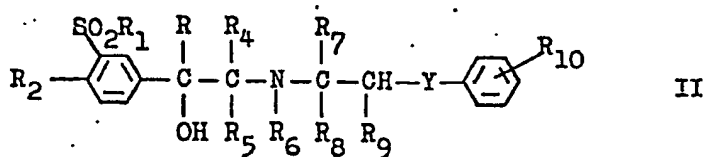
10 further, when R' of the compound shown by formula I₃ is a phenylthio group the compound can be oxidized to provide the compound shown by general formula I₄



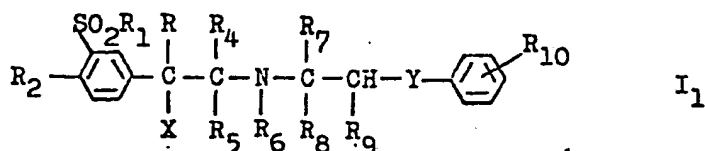
wherein R_1 , R_2 , R_4 , R_5 , R_7 , R_8 , R_9 , R_{10} and Y have the same significance as above described.

15 This process is further schematically shown below, the compounds shown by formulae I₁, I₂, I₃ and I₄ being compounds according to this invention.

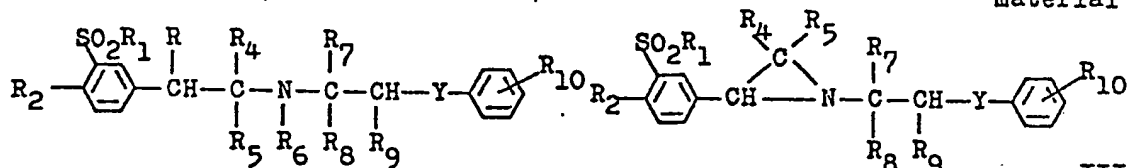
- 7 -



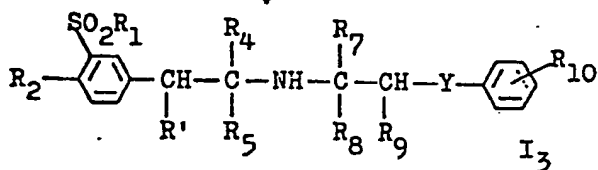
Step 1 Halogenation

Step 2
ReductionStep 3 (when R and R₆ are hydrogen)

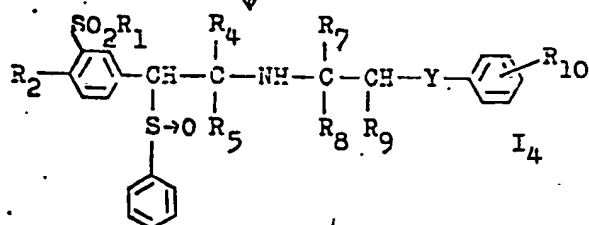
Treatment with alkaline material

I₂

Step 4 HI, lower alcohol or thiophenol



III

Step 5 (when R' is a phenylthio group)
Oxidation

- 8 -

The reaction conditions in the steps described above may be as follows:

Step 1: The halogenation of the compounds of formula II can be performed in an organic solvent such as toluene, methyl ethyl ketone, acetonitrile, tetrahydrofuran, etc., at room temperature or under heating using a halogenating agent such as thionyl chloride, hydrogen chloride, hydrogen bromide, phosphorus trichloride, phosphorus pentachloride, phosphorus oxychloride, thionyl bromide, etc.

Step 2: The reduction of the compounds of formula I_1 can be performed in an organic solvent such as methanol, ethanol, toluene, acetonitrile, tetrahydrofuran, etc., under hydrogen stream, at normal temperature and normal pressure using a catalyst such as platinum oxide, palladium carbon, etc.

Step 3: The compounds of formula III can be obtained by treating the compounds of formula I_1 (wherein, however, R and R_6 are hydrogen) with an alkaline material such as sodium carbonate, metal alcoholate, sodium hydroxide, potassium hydroxide, etc., in an organic solvent such as ethyl acetate, ^{ethanol,} dioxane, benzene, etc., at room temperature to 50°C.

Step 4:

i): The compounds of formula I_3 (wherein R' is a phenylthio group) can be obtained by reacting the compounds of formula III with thiophenol in an organic solvent such as methanol, chloroform, ethyl

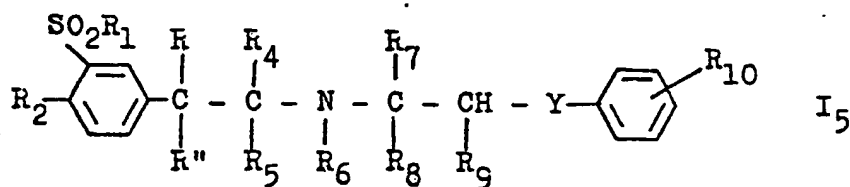
acetate, dioxane, benzene, etc., at room temperature.

ii): The compounds of formula I_3 (wherein R' is a lower alkoxy group) can be obtained by reacting the compounds of formula III with a lower alcohol in the presence of BF_3 catalyst under the same condition as in the step i).

iii): The compounds of formula I_3 (wherein R' is iodine) can be obtained by reacting the compounds of formula III with hydroiodic acid in an organic solvent such as dioxane, methanol, etc., at room temperature.

Step 5: The oxidation of the compounds of formula I_3 (wherein R' is a phenylthio group) can be performed in acetic acid at temperatures of $50-60^\circ C$ using H_2O_2 as the oxidizing agent.

In addition, among the compounds of this invention, the compounds shown by following general formula I_5



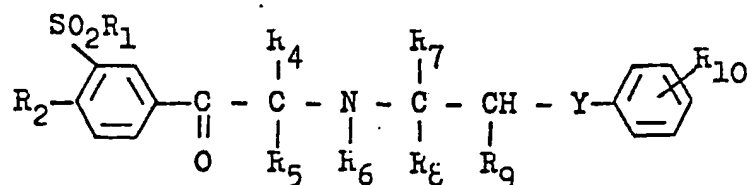
wherein R'' represents a lower alkoxy group or a phenylthio group and $R, R_1, R_2, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}$ and Y have

the same significance as above described

can be obtained by reacting the compounds of formula I_1 directly with a lower alcohol or thiophenol.

The starting materials of formula II wherein R is hydrogen used in the process of this invention are described in

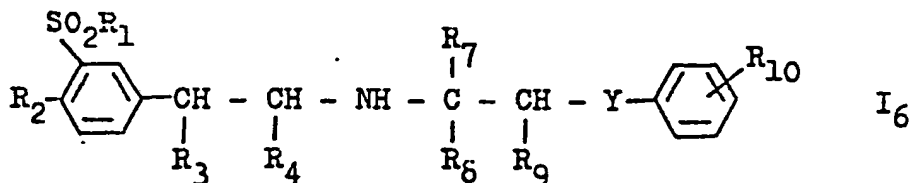
formula II wherein R is a lower alkyl group can be obtained by reacting the compounds of the following formula



described in the aforesaid British patent with a Grignard reagent (lower alkyl-MgX).

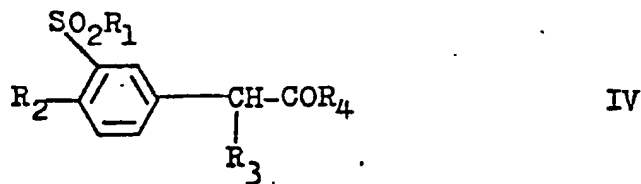
5. Process 2:

A compound of this invention shown by following general formula I₆

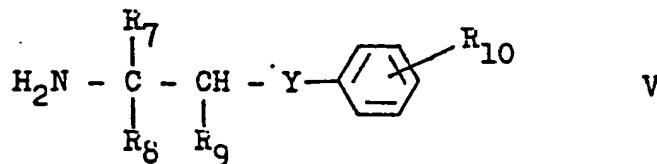


wherein R₁, R₂, R₃, R₄, R₇, R₈, R₉, R₁₀ and Y have the same significance as in formula I

10 can be produced by condensing the compounds shown by the general formulae



and



and then reducing the product thus obtained.

15 This reaction is performed by condensing the compounds of formulae IV and V in an organic solvent

such as methanol, ethanol, toluene, acetonitrile, tetrahydrofuran, etc., and then reducing the product, e.g. in the presence of PtO_2 catalyst or Raney nickel catalyst or with NaBH_4 , LiAlH_4 , etc.

The isolation and purification of the compounds of this invention shown by general formulae I_1 - I_6 and formed by Process I or 2 may be effected by filtration, extraction with a solvent, separation by column chromatography, recrystallization, etc.

The pharmacological effects of compounds of this invention were determined by the following experiments. The effects of compounds of this invention were compared with those of 5-{1-hydroxy-2-[2-(2-methoxyphenoxy)ethyl-amino]ethyl}-2-methylbenzenesulfonamide (Compound A, which is one of the typical compounds presented in British Patent No. 2,006,772 and of phentolamine.

A. α -Adrenergic blocking action:

The blood pressure was measured in rats anesthetized with urethane and treated with pentolinium. The effects of the test samples (intravenous injection - i.v.) on the hypertensive response to phenylephrine (10 $\mu\text{g}/\text{Kg}$ i.v.) were measured and the results are shown in Table I.

- 12 -

B. Antihypertensive effects in spontaneously hypertensive rats:

Oral administration (p.o.): The systolic blood pressure of spontaneously hypertensive rats having systolic blood pressure higher than 150 mmHg was measured indirectly by the tail cuff method using a programmed electrosphygmomanometer (Narco Bio-Systems Inc., PE-300), the results being shown in Table II.

Table I α -Adrenergic blocking action:

10	Sample	α -adrenergic blocking ED ₅₀ (mg/Kg) i.v.
	Compounds of this invention (Ex. No.)	
	4	0.00035
	5	0.00026
15	10	0.0059
	11	0.012
	12	0.0073
	15	0.0013
	16	0.0008
20	20	0.00000014
	25	0.0012
	26	0.004
	Known compounds	
	Compound A	0.034
25	Phentolamine	0.061

Table II Antihypertensive effect:

Sample	Dose (mg/Kg)	Change in systolic blood pressure (mmHg) at stated dose p.o.
Compounds of this invention (Ex. No.)		
10	10	-57 ± 5.6
11	30	-50 ± 4.7
12	10	-48 ± 2.0
15	10	-54 ± 6.2
16	10	-71 ± 11.1
20	3	-57 ± 4.2
25	10	-46 ± 3.6
26	10	-46 ± 4.3
Known compounds		
Compound A	10	-35 ± 6.4
Phentolamine	10	$+7.8 \pm 5.0$
"	100	-70 ± 10.1

The clinical administration of the compounds of this invention is usually practiced by intravenous injection or orally as the free bases or the acid addition salts thereof (e.g. hydrochlorides, sulfates, maleates, acetates, furates, lactates, citrates, etc.). It is appropriate to administer 10 ng - 1 mg doses of the compound several times per day in the case of intravenous administration, or 0.1 - 100 mg of the compound two or three times per day in the case of oral administration.

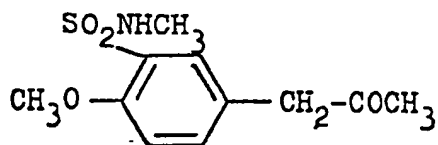
The compounds of this invention may be formulated into ordinary dosage forms such as, for example, tablets, capsules, pills, solutions, etc., and these medicaments can be prepared by conventional methods using usual medical excipients.

The production of compounds of this invention is illustrated in the following Examples.

In addition, the raw materials used in this invention include novel compounds and the production thereof is shown in Reference Examples.

- 15 -

Reference example 1.



(1) To 250 g of chlorosulfonic acid was added dropwise 50 g of 4-methoxyphenylacetone at 0-5°C. After stirring the mixture for 4 hours at room temperature, the reaction mixture was poured into 2,500 ml of ice water and extracted thrice with 500 ml of ethyl acetate. The extract was washed with water and after drying the extract with anhydrous magnesium sulfate, the solvent was distilled off under reduced pressure. The crude crystals obtained were recrystallized from benzene-ether to provide 32 g of 3-chlorosulfonyl-4-methoxyphenylacetone.

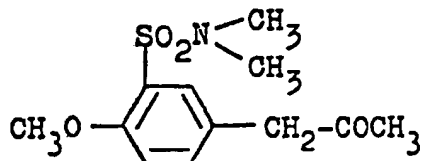
Melting point: 80-81°C

(2) In 26 ml of tetrahydrofuran was dissolved 2.6 g of 3-chlorosulfonyl-4-methoxyphenylacetone and then 1.2 g of 40% methylamine was added dropwise to the solution at a temperature lower than 10°C. After stirring the mixture for one hour at room temperature, the solvent was distilled off under reduced pressure and the residue was extracted with ethyl acetate. The extract was washed with water and after drying with anhydrous

magnesium sulfate, the solvent was distilled off under reduced pressure. The crude crystals obtained were recrystallized from isopropanol-ether to provide 1.8 g of 4-methoxy-3-N-methylsulfamylphenylacetone.

Melting point: 100-101°C.

Reference example 2.

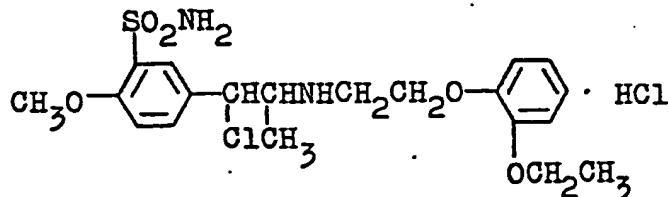


By reacting 2.6 g of 3-chlorosulfonyl-4-methoxyphenylacetone and 0.6 g of dimethylamine in the same manner as in Reference example 1-(2), 2.5 g of oily 4-methoxy-3-N,N-dimethylsulfamylphenylacetone was obtained.

Nuclear magnetic resonance spectra (CDCl₃):

δ : 2.18 (3H, s, COCH₃)
 2.82 (6H, s, N(CH₃)₂)
 3.69 (2H, s, -CH₂CO)
 3.90 (3H, s, O-CH₃)

Example 1



In 1,000 ml of acetonitrile was suspended 17 g of 5-{2-[2-(2-ethoxyphenoxy)ethylamino]-1-hydroxy-2-methylethyl}-2-methoxybenzenesulfonamide hydrochloride and while stirring the suspension, 9 g of thionyl chloride was added dropwise to the suspension

at room temperature, whereby the product first dissolved and then began to crystallize gradually. After stirring the mixture for two days, the crystals formed were recovered by filtration, washed with chloroform and dried to provide 15 g of 5-[1-chloro-2-[2-(2-ethoxyphenoxy)ethylamino]-2-methylethyl]-2-methoxybenzenesulfonamide hydrochloride.

The product has the following physicochemical properties:

Melting point: 197-200°C

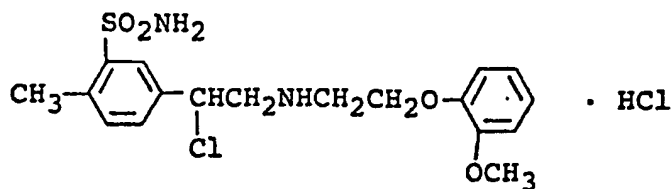
Elemental analysis for $C_{20}H_{27}N_2O_5SCl \cdot HCl$:

	C(%)	H(%)	N(%)
Calcd.:	50.11	5.89	5.84
Found :	50.06	5.96	5.95

Nuclear magnetic resonance spectra (CD_3OD):

δ :	1.30	(3H,	d,	$CH-CH_3$)
	1.40	(3H,	t,	CH_2-CH_3)
	3.63	(2H,	t,	CH_2-CH_2-N)
	4.01	(3H,	s,	$O-CH_3$)
	4.12	(2H,	q,	CH_3-CH_2-O)
	4.36	(2H,	t,	CH_2-CH_2-O)
	5.30	(1H,	d,	$Cl-CH$)

The compounds in Examples 2 and 3 were obtained in the same manner as in Example 1.

Example 2

5-{1-Chloro-2-[2-(2-methoxyphenoxy)ethylamino]ethyl}-2-methylbenzenesulfonamide hydrochloride

Physicochemical properties:

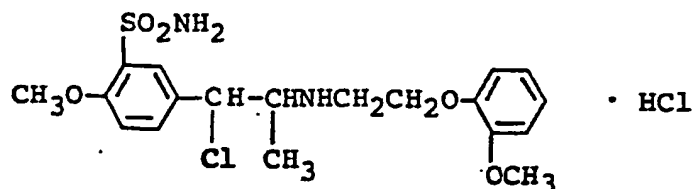
Melting point: 190-191°C

Elemental analysis for $C_{18}H_{23}N_2O_4SCl \cdot HCl$:

	C(%)	H(%)	N(%)
Calculated:	49.66	5.56	6.43
Found:	49.51	5.70	6.53

Nuclear magnetic resonance spectra (d_6 -DMSO):

δ : 2.61 (3H, s, , CH_3), 3.64 (3H, s, , OCH_3), 5.66 (1H, m, $>CH-Cl$)

Example 3

5-{1-Chloro-2-[2-(2-methoxyphenoxy)ethylamino]-2-methylethyl}-2-methoxybenzenesulfonamide hydrochloride

Physicochemical properties:

Melting point: 195-197°C (decomposed)

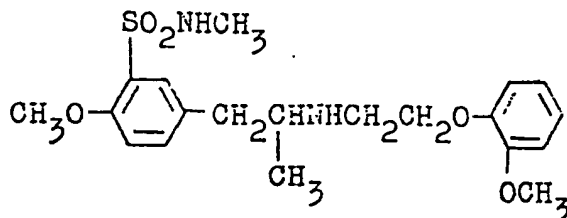
Elemental analysis for $C_{19}H_{25}N_2O_5SCl \cdot HCl$:

	C(%)	H(%)	N(%)
Calculated:	49.04	5.63	6.02
Found:	49.02	5.64	6.08

Nuclear magnetic resonance spectra ($CD_3OD + d_6$ -DMSO):

δ : 1.18 (3H, d, $>CH-CH_3$), 3.80 and 3.95 (3H + 3H, s, $-O-CH_3$), 5.56 (1H, d, $>CH-Cl$)

Example 4



A mixture of 1.4 g of 4-methoxy-3-N-methylsulfamylphenyl-
acetone, 1 g of 2-methoxyphenoxyethylamine, and 30 ml of
methanol was refluxed for one hour. After cooling the mixture,
60 mg of a platinum oxide catalyst was added thereto, and
reduction was performed at normal temperature and pressure.
After absorption of a theoretical amount of hydrogen, the catalyst
was filtered away. After the filtrate was acidified with
alcoholic 5% hydrochloric acid, the solvent was
distilled off under reduced pressure to form 1.6 g of
crystals, which were recovered and recrystallized to provide
1.2 g of the colorless crystals of 2-methoxy-5-{2-[2-(2-
methoxyphenoxy)ethylamino]-2-methylethyl}-N-methylbenzene-
sulfonamide hydrochloride.

The product has the following physicochemical properties:

Melting point: 162-163°C.

Elemental analysis for $C_{20}H_{28}N_2O_5S.HCl$:

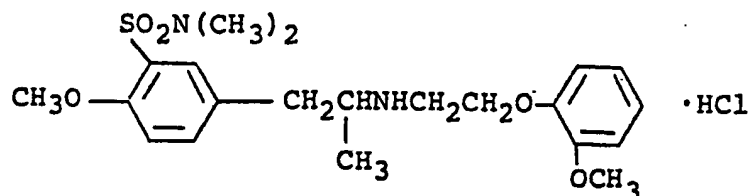
	C(%)	H(%)	N(%)
Calcd.:	53.99	6.57	6.30
Found :	53.85	6.70	6.27

Nuclear magnetic resonance spectra (d_6 -DMSO):

δ : 1.15 (3H, d, $-CHCH_3$)
3.76 and 3.88 (3H + 3H, s, $O-CH_3$)

The compound of Example 5 was obtained in the same manner as in Example 4.

Example 5



2-Methoxy-5-{2-[2-(2-methoxyphenoxy)ethylamino]-2-methylethyl}-N,N-dimethylbenzenesulfonamide hydrochloride

Physicochemical properties:

Melting point: 185-187°C

Elemental analysis for $C_{21}H_{30}N_2O_5S \cdot HCl$:

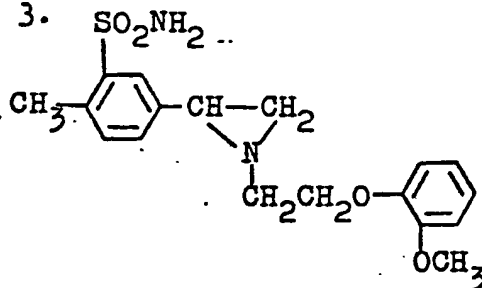
	C(%)	H(%)	N(%)
Calculated:	54.95	6.81	6.10
Found:	54.73	6.88	5.85

Nuclear magnetic resonance spectra (d_6 -DMSO):

δ : 1.16 (3H, d, $CHCH_3$), 2.71 (6H, s, $N(CH_3)_2$)

3.76 and 3.87 (3H + 3H, s, $-O-CH_3$)

Reference example 3.



In 50 ml of ethyl acetate was suspended 4.35 g (0.01 mole) of 5-{1-chloro-2-[2-(2-methoxyphenoxy)ethylamino]ethyl}-2-methylbenzenesulfonamide hydrochloride and then 50 ml of an aqueous 10% sodium carbonate solution was added to the suspension with stirring. After further stirring overnight vigorously, the reaction mixture was recovered by decantation. After removing inorganic matter by passing the ethyl acetate layer thus recovered through a silica gel column (50 ml of silica gel), the reaction product was evaporated to dryness to provide 3.2 g (88%) of colorless resinous 5-{1-[2-(2-methoxyphenoxy)-ethyl]aziridin-2-yl}-2-methylbenzenesulfonamide.

- 21 -

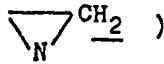
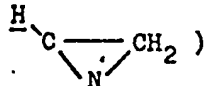
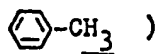
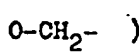
The product has the following physicochemical properties:

Amorphous form.

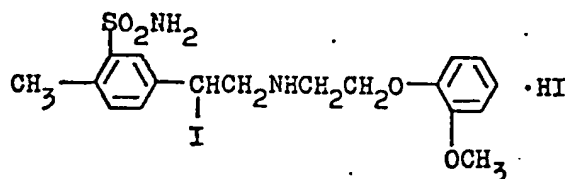
Elemental analysis for $C_{18}H_{22}N_2O_4S$:

	C(%)	H(%)	N(%)
5 Calcd.:	59.65	6.12	7.73
Found :	59.37	6.12	7.61

Nuclear magnetic resonance spectra ($CDCl_3$):

5	δ : 1.74 and 1.95	(1H + 1H, d,	)
	2.43	(1H, q,	)
10	2.55	(3H, s	)
	4.10	(2H, t,	)

Example 6



In 50 ml of dioxane was dissolved 2.5 g of 5-[1-2-(2-methoxyphenoxy)ethyl]aziridin-2-yl]-2-methylbenzenesulfonamide
 15 and after adding thereto 1 g of concentrated hydroiodic acid, the mixture was stirred overnight. After the reaction was over, the solvent was distilled off under reduced pressure and the residue was washed thrice with 30 ml of water and then
 20 thrice with 200 ml of ether and crystallized by the addition of ethyl acetate. The crystals were recovered by filtration, washed with water, and dried to provide 1.7 g of 5-[1-iodo-2-(2-methoxyphenoxy)ethyl]aziridin-2-yl]-2-methylbenzenesulfonamide hydroiodide.

The product has the following physicochemical properties:

Melting point: 154-155°C.

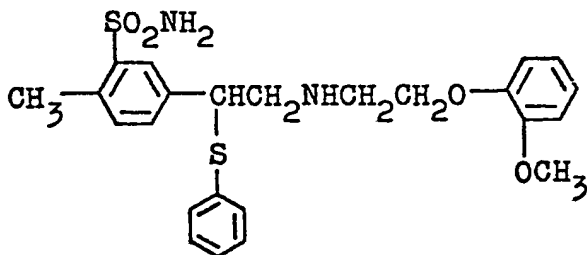
Elemental analysis for $C_{18}H_{23}N_2O_4SI.HI$:

	C(%)	H(%)	N(%)
Calcd.:	34.97	3.91	4.53
Found :	35.07	3.98	4.39

Nuclear magnetic resonance spectra (CD_3OD):

δ :	2.65	(3H, s, $\text{C}_6\text{H}_5\text{-CH}_3$)
	3.54	(2H, t, $-\text{CH}_2\text{-N-}$)
	4.30	(2H, t, $-\text{CH}_2\text{-O}$)
	5.55	(1H, t, $>\text{CH-I}$)

Example 7



In 50 ml of methanol was dissolved 2.5 g of 5-{1-[2-(2-methoxyphenoxy)ethyl]aziridin-2-yl}-2-methylbenzenesulfonamide and after adding 1 g of thiophenol to the solution and stirring the mixture overnight at room temperature, methanol was distilled off. The residue was subjected to silica gel column chromatography and the product was eluted by a mixed solvent of chloroform and methanol (9 : 1 by volume ratio) to provide 2.4 g of 5-{2-[2-(2-methoxyphenoxy)-ethylamino]-1-phenylthioethyl}-2-methylbenzenesulfonamide as a viscous oily material.

The product has the following physicochemical properties:

Amorphous form.

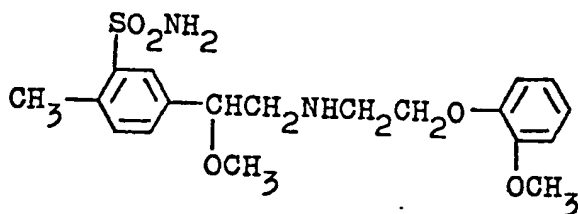
Elemental analysis for $C_{24}H_{26}N_2O_4S_2$:

	C(%)	H(%)	N(%)
Calcd.:	60.99	5.97	5.93
Found :	60.72	6.11	5.71

Nuclear magnetic resonance spectra ($CDCl_3$):

δ :	2.58	(3H, s, $\text{C}_6\text{H}_5\text{-CH}_3$)
	3.74	(3H, s, O-CH_3)
	3.98	(2H, t, $-\text{CH}_2\text{-O}$)
	4.35	(1H, t, $>\text{CH-S}$)

Example 8



In 50 ml of methanol was dissolved 2.5 g of 5-[1-[2-(2-methoxyphenoxy)ethyl]aziridin-2-yl]-2-methylbenzenesulfonamide and after adding thereto 2 ml of a boron trifluoride ether complex at room temperature, the mixture was stirred overnight. Thereafter, methanol was distilled off under reduced pressure and the residue was subjected to silica gel column chromatography and eluted with a mixed solvent of chloroform and methanol (9 : 1 by volume ratio), whereby 1.5 g of a colorless viscous oily material was obtained. The product was crystallized by the addition of 5 ml of methanol and several drops of ammonia. The crystals formed were recovered by filtration, washed with water, and dried to provide 1.2 g of

5-{1-methoxy-2-[2-(2-methoxyphenoxy)ethylamino]ethyl}-2-methylbenzenesulfonamide.



The product has the following physicochemical properties:

Melting point: 150-152°C.

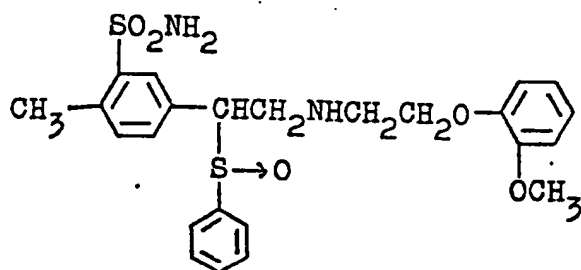
Elemental analysis for $C_{19}H_{26}N_2O_5S$:

	C(%)	H(%)	N(%)
Calcd.:	57.85	6.64	7.10
Found :	57.58	6.79	7.24

Nuclear magnetic resonance spectra (CD_3OD):

δ :	2.65	(3H, s,	 -CH ₃)
	2.98	(2H, t,	-CH ₂ N)
	3.80	(3H, s,	 -OCH ₃)
	3.26	(3H, s,	CH-OCH ₃)
	4.10	(2H, t,	-CH ₂ O)
	4.40	(1H, q,	>CH-O)

Example 9



In 20 ml of acetic acid was dissolved 2 g of 5-{2-[2-(2-methoxyphenoxy)ethylamino]-1-phenylthioethyl}-2-methylbenzenesulfonamide and after adding thereto 0.5 ml of 30% H_2O_2 , the mixture was heated to 50-60°C for 3 hours. After adding thereto 100 ml of water, the reaction mixture was extracted with 200 ml of ethyl acetate.

The ethyl acetate extract

was washed with an aqueous 1% sodium carbonate solution and then ethyl acetate was distilled off under reduced pressure. The residue was subjected to silica gel column chromatography, the product was eluted with a mixed solvent of chloroform and methanol (9 : 1 by volume ratio), and the colorless viscous oily product thus obtained was crystallized by the addition of ethyl acetate. The crystals formed were recovered by filtration to provide 1.3 g of 5-{2-[2-(2-methoxyphenoxy)-ethylamino]-1-phenylsulfinylethyl}-2-methylbenzenesulfonamide.

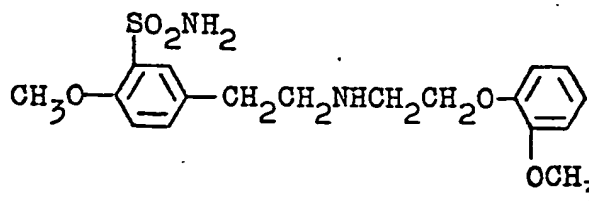
The product has the following physicochemical properties:

Melting point: 139-141°C

Elemental analysis for $C_{24}H_{28}N_2O_5S_2$:

	C(%)	H(%)	N(%)
Calcd.:	59.00	5.78	5.73
Found :	58.91	5.74	5.72

Example 10



In 150 ml of methanol was dissolved 3.8 g of 5-{1-chloro-2-[2-(2-methoxyphenoxy)ethylamino]ethyl}-2-methoxybenzenesulfonamide hydrochloride and after adding thereto 0.5 g of

0034432

10% palladium carbon, dechlorination was performed under hydrogen stream at normal temperature and pressure. The palladium carbon was filtered away and the filtrate was concentrated under reduced pressure to provide 3.1 g of 2-methoxy-5-{2-[2-(2-methoxyphenoxy)ethylamino]ethyl} benzene-sulfonamide hydrochloride, which was recrystallized from 120 ml of a mixture of methanol and ethanol (1 : 4 by volume ratio) to provide 2.3 g of the colorless crystals thereof.

The product has the following physicochemical properties:

Melting point: 196-198°C

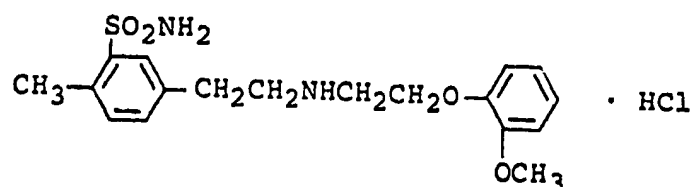
Elemental analysis for $C_{18}H_{24}N_2O_5S \cdot HCl$):

	C(%)	H(%)	N(%)
Calcd.:	51.86	6.04	6.72
Found :	51.72	6.23	6.68

Nuclear magnetic resonance spectra (CD_3OD):

δ :	3.84 and 3.98	(3H + 3H,	s,	$-OCH_3$)
	4.24	(2H,	t,	$-OCH_2-$)

The compounds in Examples 11-29 were obtained in the same manner as in Example 10.

Example 11

5- $\{2-[2-(2\text{-Methoxyphenoxy})\text{ethylamino}]\text{ethyl}\}$ -2-methylbenzenesulfonamide hydrochloride

Physicochemical properties:

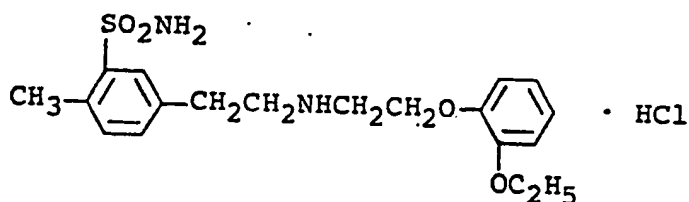
Melting point: 173-175°C

Elemental analysis for $\text{C}_{18}\text{H}_{24}\text{N}_2\text{O}_4\text{S} \cdot \text{HCl}$:

	C(%)	H(%)	N(%)
Calculated:	53.93	6.28	6.99
Found:	53.83	6.27	6.97

Nuclear magnetic resonance spectra (CD_3OD):

δ : 2.64 (3H, s, , 3.84 (3H, s,)
4.28 (2H, t,)

Example 12

5- $\{2-[2-(2\text{-Ethoxyphenoxy})\text{ethylamino}]\text{ethyl}\}$ -2-methylbenzenesulfonamide hydrochloride

Physicochemical properties:

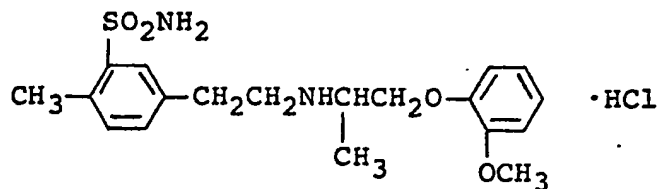
Melting point: 180-181.5°C

Elemental analysis for $\text{C}_{19}\text{H}_{26}\text{N}_2\text{O}_4\text{S} \cdot \text{HCl}$:

	C(%)	H(%)	N(%)
Calculated:	55.00	6.56	6.75
Found:	54.81	6.56	6.89

Nuclear magnetic resonance spectra (CD_3OD):

δ : 1.36 (3H, t, , 2.64 (3H, s,)
4.10 (2H, q, , 4.36 (2H, t,)

Example 13

5-{2-[2-(2-Methoxyphenoxy)-1-methylethylamino]ethyl}-2-methylbenzenesulfonamide hydrochloride


Physicochemical properties:

Melting point: 169-171°C

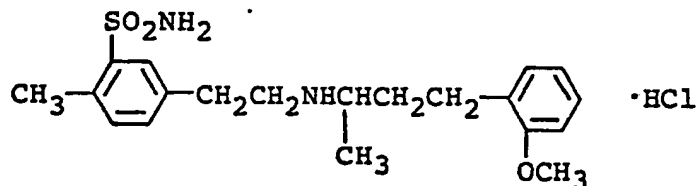
Elemental analysis for $C_{19}H_{26}N_2O_4S \cdot HCl$:

	C(%)	H(%)	N(%)
Calculated:	55.00	6.56	6.75
Found:	54.89	6.60	6.76

Nuclear magnetic resonance spectra (CD_3OD):

δ : 1.15 (3H, d, $\underline{>CH-CH_3}$), 2.64 (3H, s, $\underline{CH_3}$ -)

3.80 (3H, s, $\underline{-OCH_3}$)

Example 14

5-{2-[3-(2-Methoxyphenyl)-1-methylpropylamino]ethyl}-2-methylbenzenesulfonamide hydrochloride


Physicochemical properties:

Melting point: 198-200°C

Elemental analysis for $C_{20}H_{28}N_2O_3S \cdot HCl$:

	C(%)	H(%)	N(%)
Calculated:	58.17	7.08	6.78
Found:	58.09	7.01	6.62

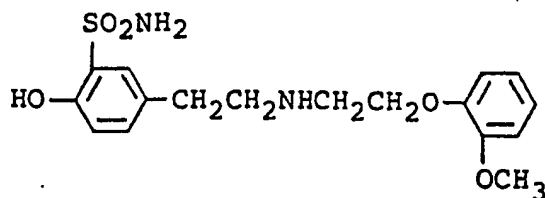
Nuclear magnetic resonance spectra (d_6 -DMSO):

δ : 1.35 (3H, d, $\underline{>CH-CH_3}$), 2.55 (3H, s, $\underline{CH_3}$ -)

3.78 (3H, s, $\underline{-OCH_3}$)

0034432

Example 15



2-Hydroxy-5-[2-[2-(2-methoxyphenoxy)ethylamino]ethyl]benzenesulfonamide

Physicochemical properties:

Melting point: 97-99°C

Elemental analysis for $C_{17}H_{22}N_2O_5S \cdot H_2O$:

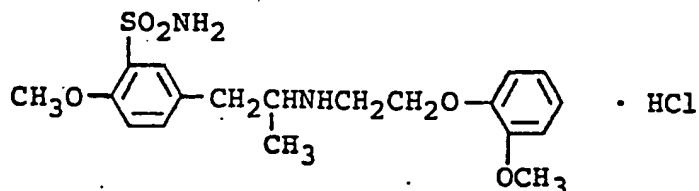
	C(%)	H(%)	N(%)
Calculated:	53.10	6.29	7.29
Found:	52.75	6.22	7.09

Nuclear magnetic resonance spectra (d_6 -DMSO):

δ : 3.76 (3H, s, $-OCH_3$)

4.04 (2H, t, $-OCH_2-$)

Example 16



2-Methoxy-5-[2-[2-(2-methoxyphenoxy)ethylamino]-2-methylethyl]benzenesulfonamide hydrochloride

Physicochemical properties:

Melting point: above 250°C

Elemental analysis for $C_{19}H_{26}N_2O_5S \cdot HCl$:

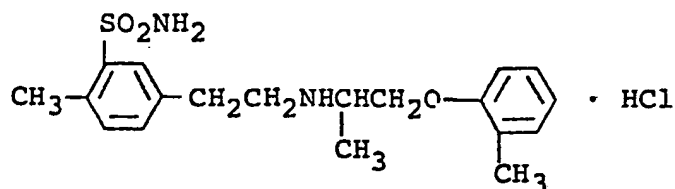
	C(%)	H(%)	N(%)
Calculated:	52.96	6.31	6.50
Found:	52.44	6.31	6.47

Nuclear magnetic resonance spectra (d_6 -DMSO):

δ 1.15 (3H, d, $>CH-CH_3$)

3.78 and 3.90 (3H + 3H, s, $-OCH_3$)

4.38 (2H, t, $-OCH_2-$)

Example 17

2-Methyl-5-[2-[2-(2-methylphenoxy)-1-methylethylamino]ethyl]-benzenesulfonamide hydrochloride

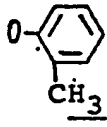

Physicochemical properties:

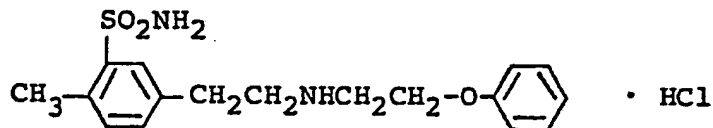
Melting point: 183-185°C

Elemental analysis for $C_{19}H_{26}N_2O_3S \cdot HCl$:

	C(%)	H(%)	N(%)
Calculated:	57.20	6.82	7.02
Found:	57.13	6.79	6.99

Nuclear magnetic resonance spectra (CD_3OD):

δ : 1.55 (3H, d, $>CH-CH_3$) 2.24 (3H, s, )
 2.64 (3H, s, )
 2.08-2.40 (2H, m, $-OCH_2-$)

Example 18

2-Methyl-5-[2-(2-phenoxyethylamino)ethyl]benzenesulfonamide hydrochloride


Physicochemical properties:

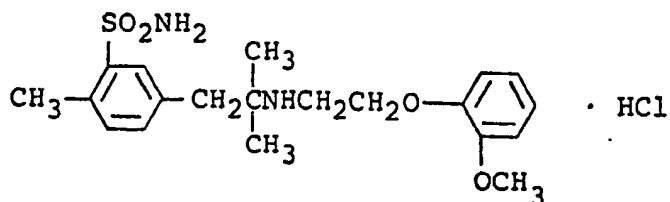
Melting point: 208.5-210°C

Elemental analysis for $C_{17}H_{22}N_2O_3S \cdot HCl$:

	C(%)	H(%)	N(%)
Calculated:	55.05	6.25	7.55
Found:	54.83	6.23	7.48

Nuclear magnetic resonance spectra (CD_3OD):

δ : 2.65 (3H, s, )
 4.32 (2H, t, $-OCH_2-$)

Example 19

5- $\{2-[2-(2\text{-Methoxyphenoxy})\text{ethylamino}]-2,2\text{-dimethylethyl}\}$ -2-methylbenzenesulfonamide hydrochloride

Physicochemical properties:

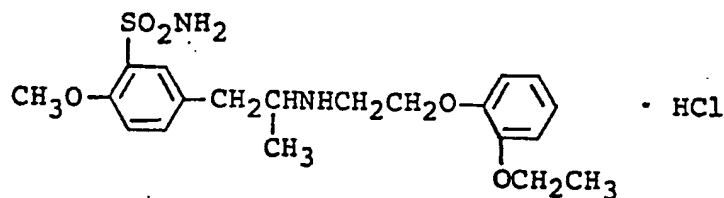
Melting point: 199-202°C

Elemental analysis for $\text{C}_{20}\text{H}_{28}\text{N}_2\text{O}_4\text{S}\cdot\text{HCl}\cdot\text{CH}_3\text{OH}$:

	C(%)	H(%)	N(%)
Calculated:	54.71	7.21	6.08
Found:	54.50	7.17	6.14

Nuclear magnetic resonance spectra (d_6 -DMSO):

δ : 1.24 (6H, s, $-\text{C}(\text{CH}_3)_2-$), 2.56 (3H, s, $\text{C}_6\text{H}_4-\text{CH}_3$)
 3.74 (3H, s, $\text{C}_6\text{H}_4-\text{OCH}_3$), 4.30 (2H, t, $-\text{CH}_2-\text{O}$)

Example 20

5- $\{2-[2-(2\text{-Ethoxyphenoxy})\text{ethylamino}]-2\text{-methylethyl}\}$ -2-methoxybenzenesulfonamide hydrochloride

Physicochemical properties:

Melting point: 254-256°C

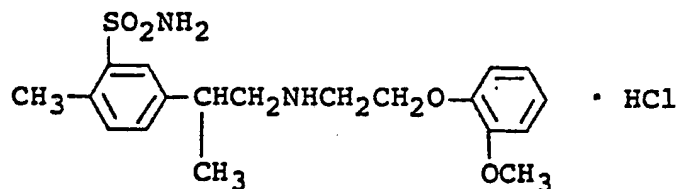
Elemental analysis for $\text{C}_{20}\text{H}_{28}\text{N}_2\text{O}_5\text{S}\cdot\text{HCl}$:

	C(%)	H(%)	N(%)
Calculated:	53.99	6.57	6.30
Found:	53.79	6.58	6.26

Nuclear magnetic resonance spectra (CD_3OD):

δ : 1.28 (3H, d, $>\text{CH}-\text{CH}_3$), 1.38 (3H, t, CH_2-CH_3)
 3.97 (3H, s, $\text{O}-\text{CH}_3$), 4.30 (2H, t, $\text{CH}_2-\text{CH}_2-\text{O}$)

Example 21



5-{2-[2-(2-Methoxyphenoxy)ethylamino]-1-methylethyl}-2-methylbenzenesulfonamide hydrochloride

Physicochemical properties:

Melting point: 183-185°C

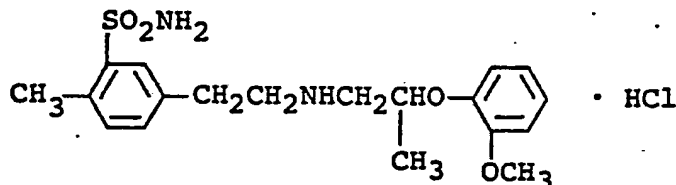
Elemental analysis for $C_{19}H_{26}N_2O_4S \cdot HCl$:

	C(%)	H(%)	N(%)
Calculated:	55.00	6.56	6.75
Found:	54.76	6.56	6.74

Nuclear magnetic resonance spectra (CD_3OD):

δ : 1.40 (3H, d, $\text{CH}-\underline{CH_3}$), 2.64 (3H, s,)
3.80 (3H, s,) , 4.23 (2H, t, $-\underline{CH_2}-O$)

Example 22



5-{2-[2-(2-Methoxyphenoxy)-2-methylethylamino]ethyl}-2-methylbenzenesulfonamide hydrochloride

Physicochemical properties:

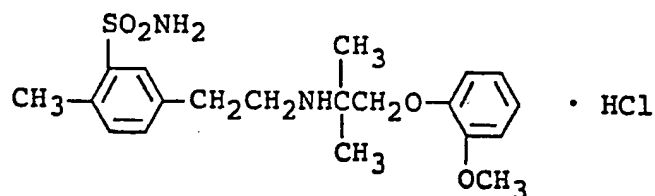
Melting point: 231-232°C

Elemental analysis for $C_{19}H_{26}N_2O_4S \cdot HCl$:

	C(%)	H(%)	N(%)
Calculated:	55.00	6.56	6.75
Found:	54.86	6.58	6.83

Nuclear magnetic resonance spectra (CD_3OD):

δ : 1.26 (3H, d, $\text{CH}-\underline{CH_3}$), 2.60 (3H, s,)
3.76 (3H, s,) , 4.42 (1H, m, $CH_3-\underline{CH}-O$)

Example 23

5-{2-[2-(2-Methoxyphenoxy)-1,1-dimethylethylamino]ethyl}-2-methylbenzenesulfonamide hydrochloride



Physicochemical properties:

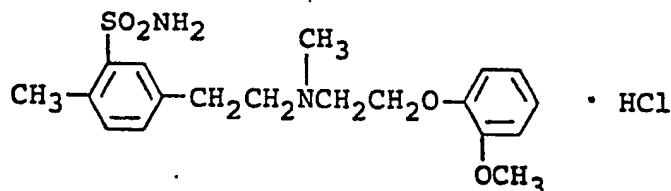
Melting point: 191-193°C

Elemental analysis for $C_{20}H_{28}N_2O_4S \cdot HCl$:

	C(%)	H(%)	N(%)
Calculated:	56.00	6.81	6.53
Found:	55.83	6.86	6.32

Nuclear magnetic resonance spectra (d_6 -DMSO):

δ : 1.44 (6H, s, $N-C(CH_3)_2-C$), 2.56 (3H, s, -CH₃)
3.66 (3H, s, -OCH₃), 4.08 (2H, s, -CH₂-O)

Example 24

5-{2-[N-[2-(2-Methoxyphenoxy)ethyl]-N-methylamino]ethyl}-2-methylbenzenesulfonamide hydrochloride



Physicochemical properties:

Melting point: 169-171°C

Elemental analysis for $C_{19}H_{26}N_2O_4S \cdot HCl$:

	C(%)	H(%)	N(%)
Calculated:	55.00	6.56	6.75
Found:	54.88	6.51	6.64

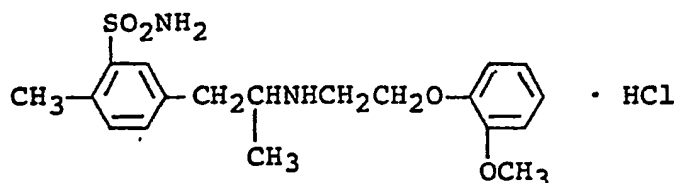
Nuclear magnetic resonance spectra (d_6 -DMSD):

δ : 2.56 (3H, s, -CH₃), 3.68 (3H, s, -OCH₃)

4.39 (2H, t, -CH₂-O)

0034432

Example 25



5- $\{2-[2-(2\text{-Methoxyphenoxy})\text{ethylamino}]-2\text{-methylethyl}\}$ -2-methylbenzenesulfonamide hydrochloride

Physicochemical properties:

Melting point: 250-252°C

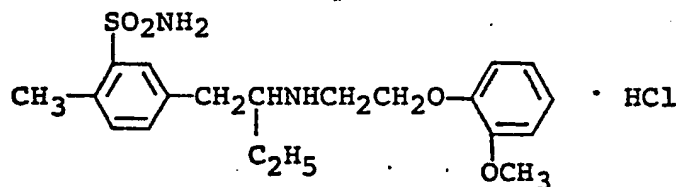
Elemental analysis for $\text{C}_{19}\text{H}_{26}\text{N}_2\text{O}_4\text{S} \cdot \text{HCl}$:

	C(%)	H(%)	N(%)
Calculated:	55.00	6.56	6.75
Found:	54.68	6.49	6.58

Nuclear magnetic resonance spectra ($\text{CDCl}_3 + \text{d}_6\text{-DMSO} + \text{D}_2\text{O} + \text{Na}_2\text{CO}_3$):

δ : 1.06 (3H, d, CHCH_3), 2.61 (3H, s, $\text{CH}_3\text{-C}_6\text{H}_4$),
3.76 (3H, s, $\text{C}_6\text{H}_4\text{-OCH}_3$)

Example 26



5- $\{2-[2-(2\text{-Methoxyphenoxy})\text{ethylamino}]-2\text{-ethylethyl}\}$ -2-methylbenzenesulfonamide hydrochloride

Physicochemical properties:

Melting point: 198-200°C

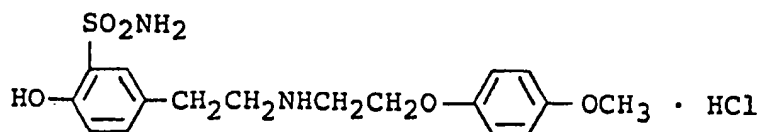
Elemental analysis for $\text{C}_{20}\text{H}_{28}\text{N}_2\text{O}_4\text{S} \cdot \text{HCl}$:

	C(%)	H(%)	N(%)
Calculated:	56.00	6.81	6.53
Found:	55.76	6.88	6.51

Nuclear magnetic resonance spectra ($\text{CDCl}_3 + \text{d}_6\text{-DMSO} + \text{D}_2\text{O} + \text{Na}_2\text{CO}_3$):

δ : 0.94 (3H, t, CHCH_2CH_3), 1.22 (2H, m, CHCH_2CH_3),
2.56 (3H, s, $\text{CH}_3\text{-C}_6\text{H}_4$), 3.76 (3H, s, $\text{C}_6\text{H}_4\text{-OCH}_3$)

Example 27



2-Hydroxy-5-[2-[2-(4-methoxyphenoxy)ethylamino]ethyl]-
benzenesulfonamide hydrochloride

Physicochemical properties:

Melting point: 237-241°C (decomposed)

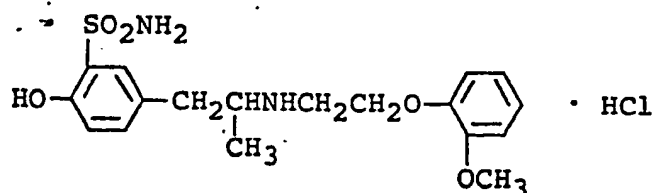
Elemental analysis for $C_{17}H_{22}N_2O_5S \cdot HCl$:

	C(%)	H(%)	N(%)
Calculated:	50.68	5.75	6.95
Found:	50.45	5.64	6.99

Nuclear magnetic resonance spectra (CD_3OD):

δ : 3.74 (3H, s, $O-\underline{CH_3}$), 4.22 (2H, t, $-\underline{CH_2}-O$)

Example 28



2-Hydroxy-5-[2-[2-(2-methoxyphenoxy)ethylamino]-2-
methylethyl]benzenesulfonamide hydrochloride

Physicochemical properties:

Melting point: 211 - 214°C

Elemental analysis for $C_{18}H_{24}N_2O_5S \cdot HCl$:

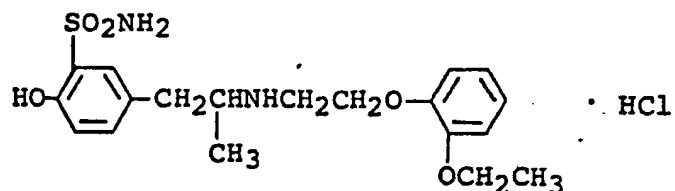
	C(%)	H(%)	N(%)
Calculated:	51.86	6.04	6.72
Found:	51.72	6.00	6.59

Nuclear magnetic resonance (CD_3OD):

δ : 1.28 (3H, d, $>\underline{CHCH_3}$), 3.86 (3H, s, $-\underline{OCH_3}$)

4.30 (2H, t, $-\underline{CH_2}-O$)

Example 29



5-{2-[2-(2-Ethoxyphenoxy)ethylamino]-2-methylethyl}-2-hydroxybenzenesulfonamide hydrochloride

Physicochemical properties:

Melting point: 172 - 173°C

Elemental analysis for $C_{19}H_{26}N_2O_5S \cdot HCl$:

	C(%)	H(%)	N(%)
Calculated:	52.96	6.31	6.50
Found:	52.83	6.65	6.12

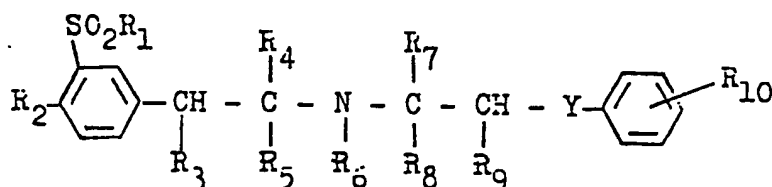
Nuclear magnetic resonance spectra (CD_3OD):

1.26 (3H, d, $\underline{>CHCH_3}$), 1.36 (3H, t, $\underline{-CH_2CH_3}$)

4.10 (2H, q, $\underline{-CH_2CH_3}$), 4.26 (2H, t, $\underline{-CH_2CH_2-O}$)

C L A I M S :

1. A sulfamoyl-substituted phenethylamine derivative represented by the general formula



wherein R_1 represents an amino group or a mono- or di-lower alkylamino group; R_2 represents a hydroxyl group, a lower alkyl group, or a lower alkoxy group; R_3 represents hydrogen, halogen, a lower alkyl group, a lower alkoxy group, a phenylthio group, or a phenylsulfinyl group; R_4 , R_5 , R_6 , R_7 , R_8 , and R_9 are selected independently from hydrogen and lower alkyl groups; R_{10} represents hydrogen, a lower alkyl group, or a lower alkoxy group; and Y represents oxygen or a methylene group and is oxygen when R_2 is a hydroxyl group; or a salt thereof.

2. A compound according to claim 1 wherein R_3 is hydrogen or a lower alkyl group.

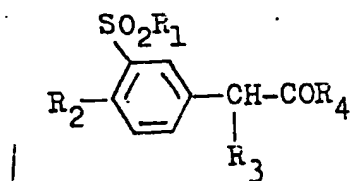
3. 5-{2-[2-(2-ethoxyphenoxy)ethylamino]-2-methylethyl}-2-methoxybenzenesulfonamide.

4. 2-methoxy-5-{2-[2-(2-methoxyphenoxy)ethylamino]-2-methylethyl}benzenesulfonamide.

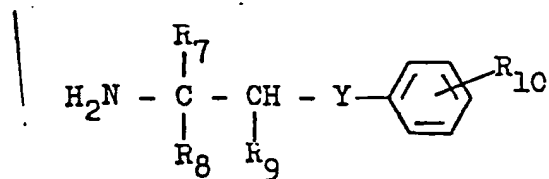
- $$\begin{array}{c} \text{SO}_2\text{R}_1 \\ | \\ \text{R}_2 - \text{C}_6\text{H}_4 - \text{C} \begin{array}{l} | \\ \text{OH} \end{array} - \text{C} \begin{array}{l} | \\ \text{R}_5 \end{array} - \text{N} \begin{array}{l} | \\ \text{R}_6 \end{array} - \text{C} \begin{array}{l} | \\ \text{R}_8 \end{array} - \text{CH} \begin{array}{l} | \\ \text{R}_9 \end{array} - \text{Y} - \text{C}_6\text{H}_4 - \text{R}_{10} \\ | \\ \text{R} \end{array}$$

wherein R represents hydrogen or a lower alkyl group and R_1 , R_2 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , and Y are as defined in claim 1 with halogenating agent and then, if desired, a) reducing the halogenated product; or b) reacting the halogenated product with a lower alcohol or thiophenol and, if desired, oxidizing the product obtained by the reaction with thiophenol; or c) reacting the halogenated product with alkaline material and then reacting the product thus obtained with hydrogen iodide, a lower alcohol, or thiophenol, and if desired, oxidizing the product obtained by the reaction with thiophenol.

10. A process of producing a compound according to claim 1, wherein R_5 and R_6 are hydrogen, which comprises condensing a compound represented by the general formula



with a compound represented by the general formula



wherein R_1 , R_2 , R_3 , R_4 , R_7 , R_8 , R_9 , R_{10} and Y are as defined in claim 1 and then reducing the condensation product.

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ BLACK BORDERS
- ☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☐ FADED TEXT OR DRAWING
- ☐ BLURRED OR ILLEGIBLE TEXT OR DRAWING
- ☐ SKEWED/SLANTED IMAGES
- ☐ COLOR OR BLACK AND WHITE PHOTOGRAPHS
- ☐ GRAY SCALE DOCUMENTS
- ☒ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☒ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☐ OTHER: _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.